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09/857,448	06/04/2001	Patrick Midoux	USB98ASIDM	3117

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EXAMINER

SCHNIZER, RICHARD A

ART UNIT

PAPER NUMBER

1635

12

DATE MAILED: 07/15/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

## Office Action Summary

Application No.  
**09/857,448**

Applicant(s)  
**Midoux**

Examiner  
**Richard Schnizer**

Art Unit  
**1635**

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on Apr 29, 2003.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 1-19 is/are pending in the application.
- 4a) Of the above, claim(s) 15, 16, and 18 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-14, 17, and 19 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claims \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on Jun 4, 2001 is/are a) ☒ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on \_\_\_\_\_ is: a) ☐ approved b) ☐ disapproved by the Examiner.  
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

### Priority under 35 U.S.C. §§ 119 and 120

- 13) ☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some\* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
  - ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  - ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\*See the attached detailed Office action for a list of the certified copies not received.

- 14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

### Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). \_\_\_\_\_
- 4) ☐ Interview Summary (PTO-413) Paper No(s). \_\_\_\_\_
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other:

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### **DETAILED ACTION**

An amendment was received and entered as Paper No. 11 on 4/29/03.

Claims 1-19 are pending in the application.

Claims 15, 16, and 18 were withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 8. The elected invention is limited to claims 1-14, 17, and 19, drawn to compositions comprising an oligomeric conjugate and an oligonucleotide, and a first method of using the composition.

### ***Specification***

The specification is objected to because it contains numerous grammatical and spelling errors. For example, page 2 contains the following misspellings and grammatical errors; “n” at line 5; insertion of “of” at line 7; the ungrammatical phrase “substituted at least 10% advantageously from 15 % to 35%” at line 8; “positivly” at line 14, “An other” at line 17, and “sialytaded” at line 26. Applicant should thoroughly review the specification for spelling and grammatical errors and correct such errors, taking care to avoid the introduction of new matter into the disclosure.

### ***Rejections and Objections Overcome***

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The objections to the claims set forth in Paper No. 9 are overcome by Applicant's amendments. The rejections of claims 1-4 under 35 USC 112, second paragraph are overcome by Applicant's amendments, but these amendments raise new grounds of rejections under 35 USC 112, as discussed below.

### ***Claim Objections***

Claim 5 is objected to because it contains unnecessary carriage returns. For example, the carriage returns immediately preceding "2-carboxy-imidazole" and "2-(1-methyl-imidazol-4yl)ethylamine" are not required and produce unnecessary spaces in the claim.

Claims 6 and 7 are objected to because the purpose of the asterisk immediately following "Flu being a fluorescent molecule" is unclear, and it appears to be unnecessary. Also, these claims use "=" and "is" interchangeably for the same purpose in definitions. See e.g. page 5, immediately following "Wherein". The claim would be clearer if one or the other of these conventions were used, but not both. Claim 6 is also objected to because "Wherein", immediately preceding the asterisk at page 5, should not be capitalized.

Claim 19 is objected to because "destabilizaiton" is misspelled, and because it lacks a comma after "cellular membranes".

Claims 9-13, 17, and 19 are objected to because they embrace nonelected subject matter, e.g. compositions comprising biological molecules other than oligonucleotides, and methods of delivering biological molecules other than oligonucleotides.

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***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-14, 17, and 19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-14, 17, and 19 are indefinite because it is unclear what is meant by “substituted”. For example, it is unclear what is intended by “substituted in the phrase “the free  $\text{NH}_3^+$  of said monomeric components are substituted in a ratio of at least 50%.” If one understands “substituted” to mean “entirely replaced by another group”, then the claim is indefinite because it requires at least 50% of the monomeric units to have a “free  $\text{NH}_3^+$ ”, while simultaneously requiring at least 50% of these “free  $\text{NH}_3^+$ ” to be replaced by another group. This is clearly not possible. If one understands “substituted” free  $\text{NH}_3^+$  to mean  $\text{NH}_3^+$  covalently bound to a monomeric component, then all “free  $\text{NH}_3^+$ ” groups in the oligomer must be “substituted” because they are attached to a monomer. In this interpretation, the limitation requiring that at least 50% of the free  $\text{NH}_3^+$  groups must be substituted loses its meaning because all  $\text{NH}_3^+$  groups are substituted by their attachment to the monomer. Alternatively, if “substituted” means that a second substituent group is covalently added to the  $\text{NH}_3^+$ , then the claim recites a non-sequitur because it would require at least 50% of the monomeric components to have a free  $\text{NH}_3^+$ , but simultaneously require that at least 50% of “the free  $\text{NH}_3^+$  of said monomeric components” to be

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further substituted. It is not possible for an oligomer to simultaneously comprise at least 50% monomeric components with a free  $\text{NH}_3^+$ , when at least 50% of those free  $\text{NH}_3^+$  must have a second substituent. This would require either a change in the valence of nitrogen to allow formation of a fifth bond, or the replacement of a H atom with the second substituent. Either way, the claim limitation requiring at least 50% of monomers to have “free  $\text{NH}_3^+$ ” could not be met.

Claim 2 is rejected because the phrase “wherein the protonable residues leading to a destabilization of cellular membranes wherein said protonable residues have a pK in aqueous medium lower than 8.0” is nonsensical. Deletion of “wherein said protonable residues” is suggested.

Claim 6 is indefinite because although “i” is defined as the degree of polymerization in the structure set forth in the claim, the structure contains no character “i”, only “ai”, “bi”, and “i-2”.

Claims 6-9 are indefinite because while they require that R represents certain structures in certain ratios, they fail to define what constitutes the ratio. In other words, if Applicant intends that 50-100% of all R groups are chosen from one set of structures, whereas 0-50% of all R groups are chosen from another set of structures, the claims do not clearly convey this because it is not clear that the recited “ratio” represents the totality of R groups. For example, the intended ratio could be a fraction of the molecular weight of the oligomer. It is suggested that the phrase “R represents in a ratio of 50% to 100% (corresponding to a number u)”, should be rewritten as “wherein 50% to 100% of all R groups (corresponding to a number u) are selected from the

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group consisting of” followed by the structures and limitations shown at pages 5-6 of Paper No.

11. It is further suggested that the phrase “\* R represents in a ratio of 0% to 50% (corresponding to f:  $0 < f \leq u$ )” should be rewritten as “and wherein and 0% to 50% of all R groups (corresponding to f, wherein:  $0 < f \leq u$ ) are selected from the group consisting of” followed by the structures and limitations shown at pages 6-7 of Paper No. 11.

As written, the claim presents two different definitions of R that could be interpreted as alternatives. definitions that do not necessarily account for the totality of all R groups in the structure.

Claims 6-9 are also indefinite because it is unclear what are the metes and bounds of the structures of the claimed oligomeric conjugates, because the claims are written with poor grammar and punctuation. For example, the structures of R' and R are unclear. At page 6 of Paper No. 11, R' is defined as representing  $\text{NH}_3^+$ , or NH substituted by a list of structures. However, the list is not set forth as a proper Markush group (see MPEP 21173.05(h)(a)), many of the members of the list are not separated by any punctuation, and the members of the list are not explicitly listed as alternatives, so it appears that R' must be all of the members of the list simultaneously. This is not possible. Similarly, R is defined as representing  $\text{NH}_3^+$ , or NH substituted by a list of structures that are not presented as alternatives. Similar claim structure appears in claims 7 and 8 which present lists of structures but do not make it clear as to whether these structures are alternatives of each other.

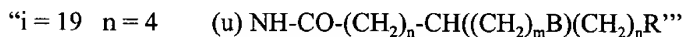
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Claims 6-9 are indefinite because the arithmetic functions recited at the end of claim 7 are not valid for all embraced values of the recited variables. For example, the claims recite the following function: total number of alpha  $\text{NH}_3^+$  =  $p = u - q$ , where  $u$  may be defined as the ratio of  $R$  groups comprising a weak base with an alpha  $\text{NH}_3^+$ , and  $q$  may be defined as the number of  $R'$  groups lacking a  $\text{NH}_3^+$  group. For an oligomer of 36 monomers where  $u = 50\%$ ,  $q$  must = 18. The recited formula would require that the total number of alpha  $\text{NH}_3^+$  groups would be  $u - q = 50 - 18 = 32$ , or  $0.5 - 18 = -17.5$ , depending on whether the ratio ' $u$ ' is expressed as a percentage or a fraction. However, the correct total number of alpha  $\text{NH}_3^+$  in this example is not 32 or -17.5, but rather 18, i.e. the number of side chain alpha  $\text{NH}_3^+$  groups. Thus the formula is not valid for all embraced values of  $u$  and  $q$ . Similarly, the formula "total number of omega  $\text{NH}_3^+ = j = f - (k + h)$  is not valid for all embraced values of the recited variables.

Claims 6-9 are indefinite because none of claims 6-8 ends in a period. Claim 9 is indefinite because it depends from claims 7 and 8.

Claims 7-9 are indefinite because although "i" is defined as the degree of polymerization in the structure set forth in the claims, the structure contains no character "i", only "i-2".

Claims 8 and 9 are also indefinite for the following reason. At pages 11-15 of Paper No. 11, claim 8 defines variables listed in claim 7, i.e.:



It is unclear what is intended by 'u' in these lists. It appears that applicant intends 'u' to be a structure, as shown above. However, as initially expressed in claim 6, 'u' is not a structure, 'u'



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represents a number of groups R present in an oligomer. For this reason it is not clear what is intended by the recitations of 'u' in claim 8. Claim 9 is included in this rejection because it depends from claim 8.

Claim 14 is indefinite because it recites "the cell nucleus" without antecedent basis. Substitution of "a" for "the" in each instance of this phrase is suggested. It is unclear what is intended by the phrase "blocks the complementary RNA sequence". Specifically, it is unclear what is intended by "blocks". Generally antisense oligonucleotides inhibit expression of complementary mRNAs. The intended metes and bounds of "blocks" are unclear and this term could be interpreted as embracing processes such as inhibiting mRNA transcription, processing, or transport. Deletion of the phrase "and blocks" is suggested. The metes and bounds of "messenger" are unclear. Does Applicant intend to limit the scope only to messenger RNA, or are other messengers, such as second messengers and other signal transduction molecules embraced? Claim 14 is also indefinite because it recites "the corresponding gene" without antecedent basis. It is unclear as to whether "the gene" must correspond to "an oligonucleotide" or "a messenger", and it is unclear in what way it must correspond. Also it is unclear, for several reasons, what are the metes and bounds of "oligonucleotides corresponding to a repetitive bacterial type DNA sequence with stimulating or immunodepressive activity." It is unclear in what way the oligonucleotide must correspond to any sequence. The metes and bounds of "repetitive bacterial type DNA sequence" are unclear. What is a bacterial type DNA? How is it distinguished from any other type of DNA? The metes and bounds of stimulating activity are

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unclear. What is to be stimulated by the DNA sequence, how, and how much? Also, the clause “oligonucleotides corresponding to a repetitive bacterial type DNA sequence with stimulating or immunodepressive activity” is presented as an alternative in a series of alternative methods, but it recites no active method steps that would accomplish the purpose set forth in the preamble, thus rendering the claim indefinite. The clause “oligonucleotides are transferred into a cytosol and/or cell nucleus which inhibit gene expression” is indefinite because it requires that gene expression is inhibited by a cytosol or a cell nucleus. The specification does not contemplate the use of a cytosols or cell nucleus for inhibition of gene expression, rather oligonucleotides are contemplated for this purpose. It is suggested that the phrase “which inhibit gene expression” should be deleted and reinserted immediately after the word “oligonucleotides”. Finally, claim 14 recites “the specific DNA region” and “the mRNA” without antecedent basis.

Claim 19 is incomprehensible. The metes and bounds of the claim are unclear because it is unclear what group or groups should be substituted, and to what extent. As such it is not clear what limitations of claim 1 pertain to claim 19. Does the “substituted by protonable” limitation of claim 19 supersede the requirement in claim 1 that some monomeric components must have  $\text{NH}_3^+$  groups? For example, does claim 19 allow any monomer of the oligomer of claim 1 to be substituted by histidine such that the oligomer is an oligohistidine? The phrase “previously fixed” is confusing. The claim does not set forth any standard point in time from which one can determine what is previous and what is not. One of skill in the art is left to ask: previously to what?

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It is noted that the claims remain so indefinite that no meaningful search of the prior art could be conducted.

***Conclusion***

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

This application contains claims 15, 16, and 18 drawn to an invention nonelected with traverse in Paper No. 8, and claims 9-13, 17, and 19 which recite nonelected embodiments. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.


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Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 703-306-5441. The examiner can normally be reached Monday through Friday between the hours of 6:20 AM and 3:50 PM. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John Leguyader, can be reached at 703-308-0447. The FAX numbers for art unit 1632 are 703-308-4242, and 703-305-3014. Additionally correspondence can be transmitted to the following RIGHTFAX numbers: 703-872-9306 for correspondence before final rejection, and 703-872-9307 for correspondence after final rejection.

Inquiries of a general nature or relating to the status of the application should be directed to the Patent Analyst Trina Turner whose telephone number is 703-305-3413.

Richard Schnizer, Ph.D.



DAVE T. NGUYEN  
PRIMARY EXAMINER